BONE STRENGTHENING AGENTS

BY Dr /Aliaa Omar El-hady

BONE STRENGTHENING AGENTS (1)
==========

Q- What nonpharmacological measures help to prevent and treat osteoporosis?

1-Adequate calcium intake (diet plus supplements):
1000 to 1200 mg/day, premenopausal women and men;
1200 to 1500 mg/day, postmenopausal women and men ≥ age 65 years.

2-Adequate vitamin D intake:
800 to 1200 international units/day.

N.B.
-Taking more than the stated amounts of calcium and vitamin D is not recommended.
-Higher amounts may be associated with more kidney stones as well as more vascular calcifications, particularly in patients with renal insufficiency.
-Vitamin D3 and vitamin D2 are equivalent when taken on a chronic basis.

3-Regular exercise: aerobic and resistance.

4-Limitation of alcohol consumption to ≤2 drinks/day.

5-Limitation of caffeine consumption to ≤2 servings/day.

6-Smoking cessation.

7-Fall prevention.

Universal Strategies
Nonpharmacologic

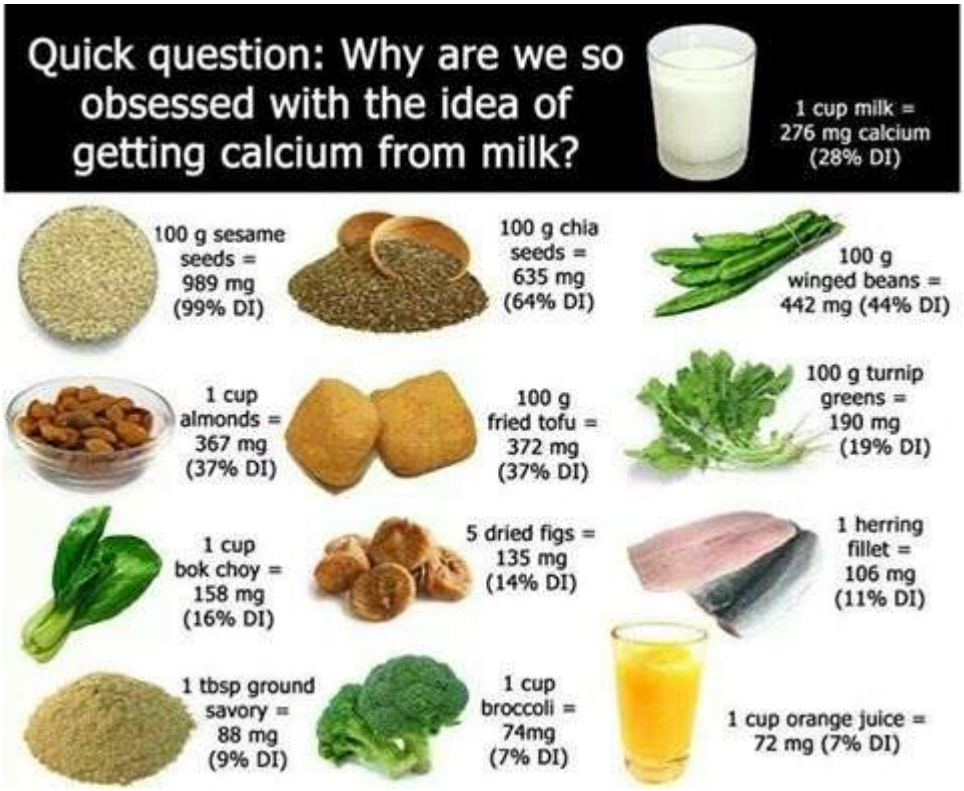
- Good general nutrition
- Adequate calcium through diet/supplementation
- Adequate vitamin D through sunlight/diet/supplementation
  - achieve 25(OH)D levels $\geq$ 30 ng/mL
- Regular weight-bearing exercise
- Avoid tobacco & excessive consumption of alcohol
- Fall prevention strategies
  - balance/gait assessment, home safety

BONE STRENGTHENING AGENTS (2)
==========
How can dietary calcium intake be accurately assessed?
نحسب ازای تقریبا احتیاج الجسم من الکالسیوم عن طریق الطعام؟؟
-The major bioavailable sources are dairy products and calcium-fortified fruit drinks.

-The following approximate calcium contents should be assigned for dairy product intake:

-Milk/yogurt 300 mg/cup
-Cheese 300 mg/oz
-Fruit juice with calcium 300 mg/cup

In addition to calcium from dairy, add another 300 mg for the general nondairy diet for a reasonable estimate
of total daily calcium intake.



BONE STRENGTHENING AGENTS (3)
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How do you ensure adequate intake of calcium?

Low-fat dairy products are the best sources of calcium.

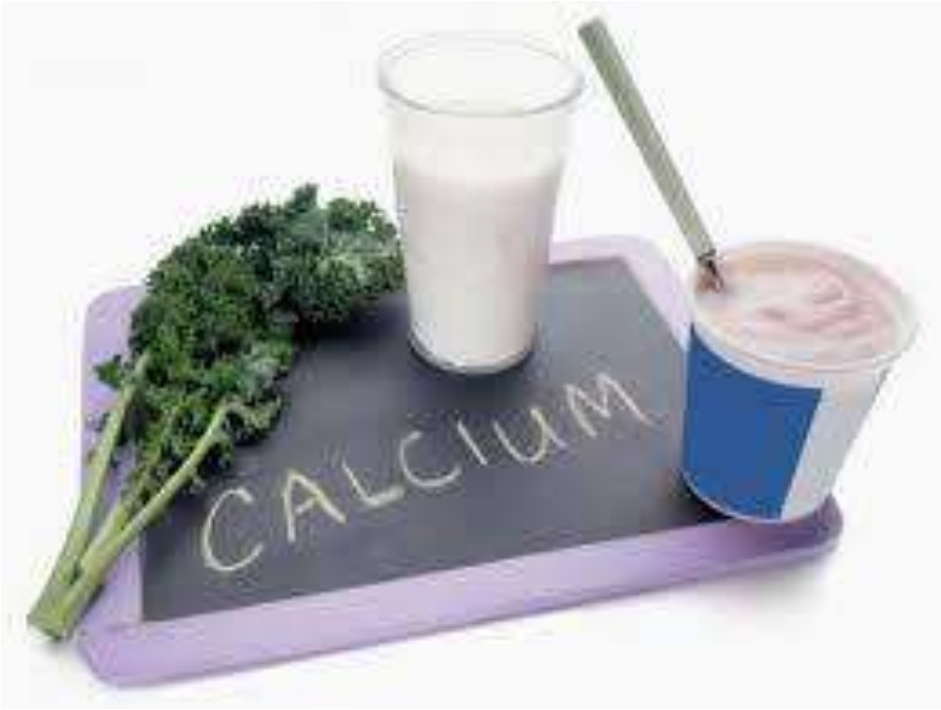
Calcium supplements should be added when the desired goals cannot be reached with dietary sources.

Calcium carbonate and calcium citrate are both well absorbed
when taken with meals. والسترات افضل يتاخد على معدة فاضية

Gastric acid is needed for normal calcium absorption; calcium carbonate absorption may be significantly reduced in patients who have achlorhydria or who use a proton pump inhibitor (PPI).

Calcium citrate absorption is less likely to be affected by PPI use.

Calcium citrate is also a better choice in patients with a history of kidney stones because citric acid is often low in the urine of stone formers.



BONE STRENGTHENING AGENTS (4)

What are the best ways to achieve adequate vitamin D intake?

There are two natural forms of vitamin D: cholecalciferol (D3) and ergocalciferol (D2).

Fatty fish (D3) (400 international units/3.5 oz), fortified milk (400 international units/quart), and cereal products (50 international units/cup) are good dietary sources.

Vitamin D2 and vitamin D3 supplements are available over the counter in multiple doses and 50,000 international units of vitamin D2 supplements can be given by prescription.

Ten minutes of midday summer sunlight exposure to a fair-skinned person in a tank top and shorts not wearing sunscreen produces 10,000 international units of vitamin D3.

Dark-skinned individuals and elderly get less production.

However, many individuals wear sunscreen (SPF >8) which prevents vitamin D production by the skin. Therefore, oral vitamin D is necessary for most people.

The optimal vitamin D intake is 800 to 1200 international units daily and should not exceed 4000 international units/day chronically.

Sources For Vitamin D3

BONE STRENGTHENING AGENTS (5)
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The goal serum 25-hydroxy vitamin D (25 OH vitamin D) level is 30 to 100 ng/mL.
In general, 1000 units daily of vitamin D will raise the serum level by 6 to 10 ng/mL.

25 OH D level	*Management*
20 to 30 ng/mL	2000 units of D3 daily
10 to 20 ng/mL	50,000 units of D2 weekly for 3 months, then 2000 units of D3 daily
<10 ng/mL	50,000 units of D2 twice weekly for 3 months, then 2000 units of D3 daily

Patients with malabsorption syndromes, bowel bypass surgery, and severe liver disease may require higher doses. Some may need to be treated with calcitriol. However, noncompliance is the most common reason that patients with persistently low vitamin D levels on therapy do not increase their levels.

BONE STRENGTHENING AGENTS (6)
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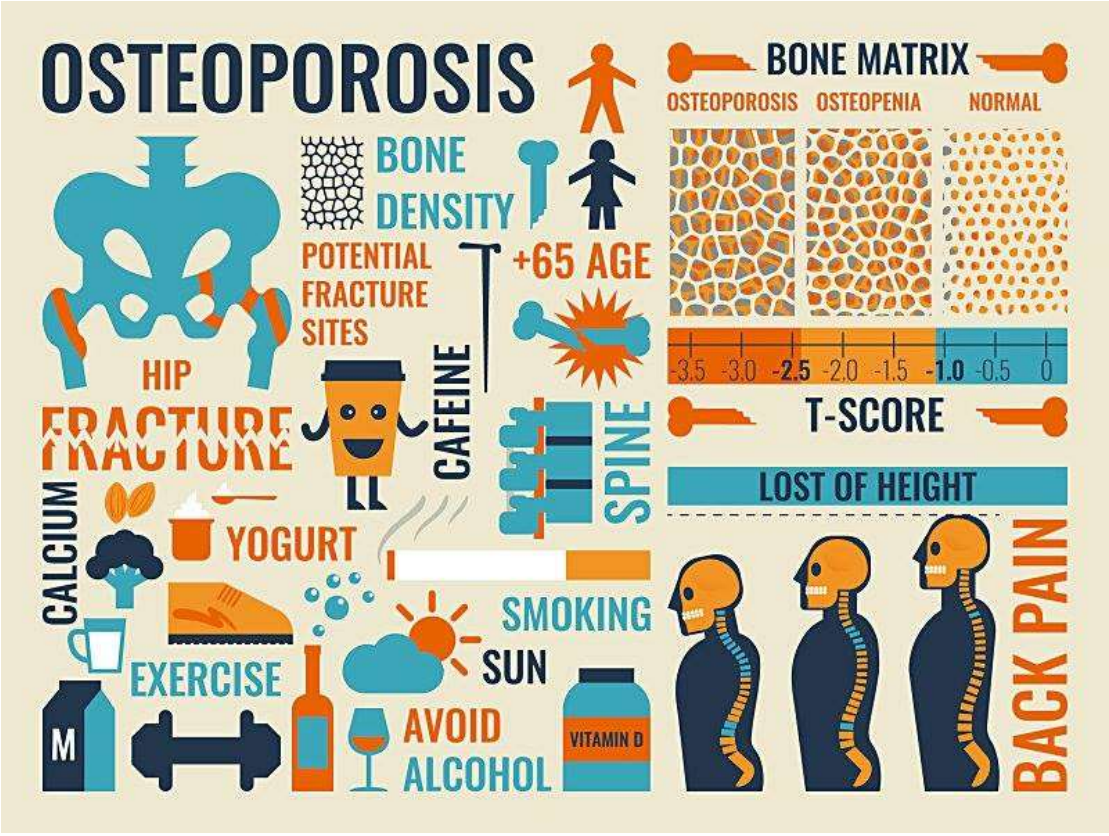
Q- When should pharmacological therapy be initiated for osteoporosis?

Pharmacological therapy should be advised for anyone who has any one of the following:

• History of vertebral or hip fragility fracture (also should include wrist and humerus).

• T-score < –2.5.

• The FRAX tool , developed by the WHO, is recommended for making treatment decisions in drug-naïve patients with osteopenia.
Treatment is advised for those who have a 10-year risk of ≥3% for hip fracture or ≥20% for other major osteoporosis fractures.



BONE STRENGTHENING AGENTS (7)
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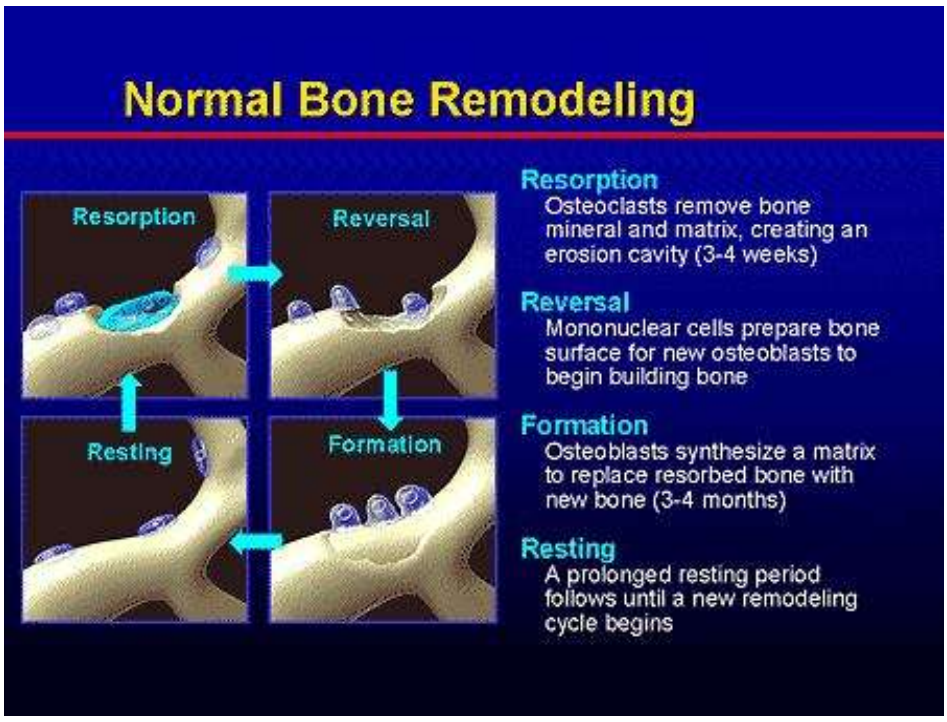
Q-Describe bone remodeling.

Bone remodeling is the process that removes old bone and replaces it with new bone.
Osteoclasts attach to bone surfaces and secrete acid and enzymes that dissolve away underlying bone.

Osteoblasts then migrate into these resorption pits and secrete osteoid, which becomes mineralized with calcium phosphate crystals (hydroxyapatite).

Osteocytes serve as the mechanoreceptors that sense skeletal stress and send signals to orchestrate the process of bone remodeling in areas of bone that need renewal.

Bone remodeling.
Osteoclasts resorb old bone, leaving an empty resorption pit.
Osteoblasts then fill the pit by secreting osteoid, which is subsequently mineralized by calcium and phosphate from the extracellular fluid, forming new bone.



BONE STRENGTHENING AGENTS (8)
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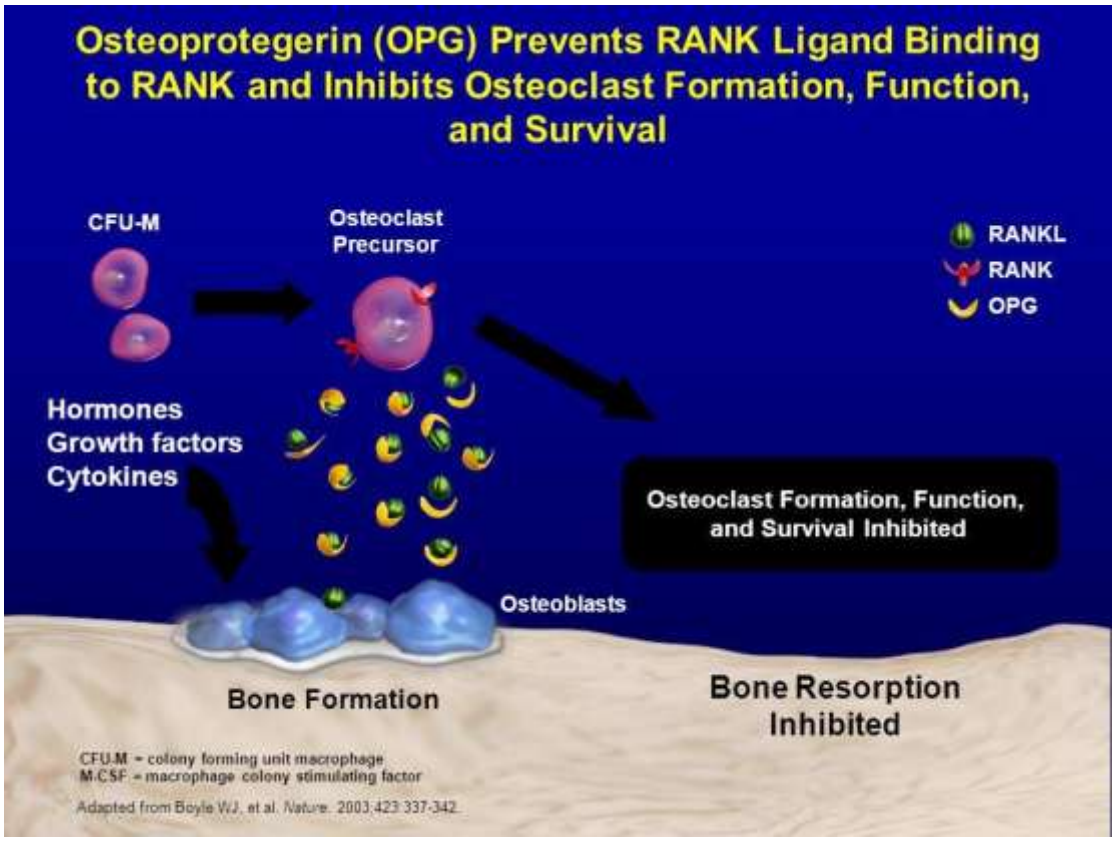
Q- What are RANK, RANK-L, and osteoprotegerin?

RANK (receptor activator of nuclear factor κ) is a specific receptor on osteoclasts.
RANK-L (RANK ligand) on osteoblasts binds to RANK to stimulate osteoclastic bone resorption.

Osteoprotegerin (OPG) is a soluble decoy receptor produced by osteoblasts and bone marrow stromal cells that binds to RANK-L, preventing it from binding to RANK.

Bone resorption is driven by RANK-L and inhibited by OPG.



BONE STRENGTHENING AGENTS (9)
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Osteoporosis medications are classified into two main categories: antiresorptive agents and anabolic agents. Antiresorptive medications include the bisphosphonates, denosumab, raloxifene, calcitonin, and estrogens. Teriparatide is the only currently available anabolic agent.

Table 87-1. Pharmacological Agents That Are FDA-Approved

MECHANISM	ROUTE	DOSE	FREQUENCY
Antiresorptive agents			
Bisphosphonates			
Alendronate (Fosamax)*	Oral	10 mg	Daily
	70 mg	Weekly	
Risedronate (Actonel)*	Oral	5 mg	Daily
		35 mg	Weekly
		150 mg	Monthly
Ibandronate (Boniva)	Oral	150 mg	Monthly
	IV	3 mg	Every 3 months
Zoledronic acid (Reclast)	IV	5 mg	Yearly
Nonbisphosphonates			
Denosumab (Prolia)	SC	60 mg	Every 6 months
Raloxifene (Evista)	Oral	60 mg	Daily
Calcitonin (Miacalcin)	Nasal	200 units	Daily
	SC*	1 00 units	Daily
Estrogen therapy (multiple preparations and regimens)			
Anabolic agents			
Teriparatide (Forteo)	SC†	20 µg	Daily

IV, Intravenous; SC, subcutaneous.
*Note that there is a Fosamax plus D preparation containing 70 mg of alendronate and either 2800 international units or 5600 international units of vitamin D3. There is also a 35-mg delayed release form of risedronate (Atelvia), which is given immediately after breakfast.
†Infusion times: IV ibandronate, 1 to 3 minutes; IV zoledronic acid, 15 to 30 minutes.

BONE STRENGTHENING AGENTS-

Bisphosphonates(10)

==========

Q-Explain how bisphosphonates are taken and why they work for osteoporosis?

-The oral nitrogenous bisphosphonates are analogs of pyrophosphate and thus they avidly bind to bone.

-They have very poor intestinal absorption (<1%) that is further inhibited by the presence of food or medications in the GIT.

-Their major side effect is esophageal and GIT pain.

-To maximize intestinal absorption and to minimize GIT toxicity, they should be taken first thing each morning on an empty stomach with a full glass of water.

-The patient should then remain upright and take nothing by mouth for at least 30 to 60 minutes after medication ingestion.

-The absorbed bisphosphonate goes through the bloodstream
and binds to bone with a terminal half-life in bone of up to 10 years.

- Approximately 50% to 60% of a dose does not bind to bone and is excreted unchanged in the urine.

-There are no drug interactions.

-Some of the bisphosphonate adsorbed to bone is ingested by the osteoclast during bone remodeling.

-The bisphosphonate acts on the osteoclast by binding and blocking the intracellular enzyme, farnesyl diphosphate synthase (FPPS), in the HMG CoA-reductase pathway (also known as the mevalonate pathway).

-Disruption of this pathway at the level of FPPS prevents the formation of two metabolites that are essential for connecting some small proteins (Ras, Rho,Rac) to the cell

membrane, a process known as prenylation, which is important for proper subcellular protein trafficking.

-This interferes with lipid modification of the osteoclast cell membrane/cytoskeleton that is needed for maintaining the “ruffled border.”

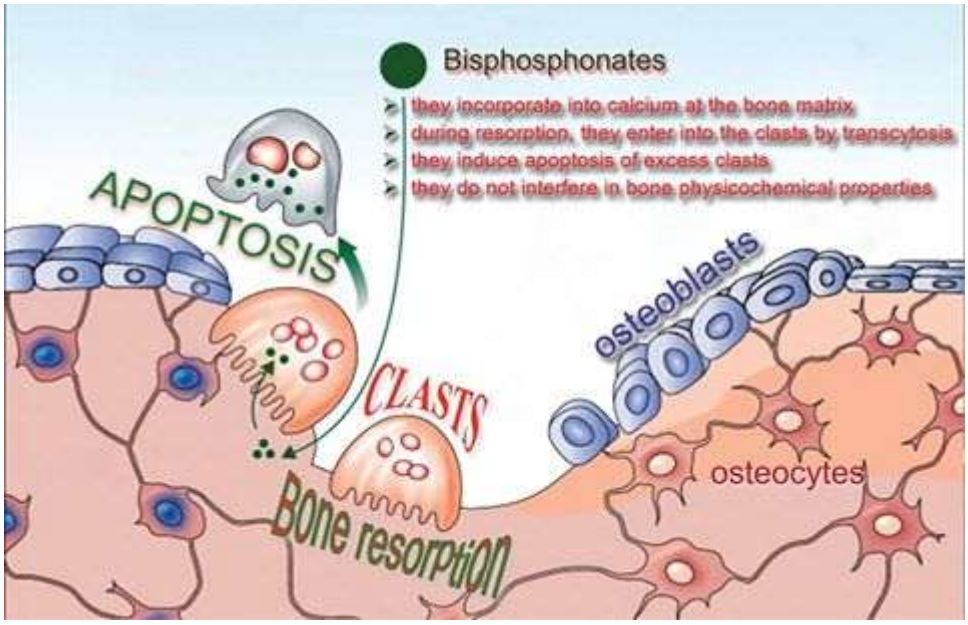
-This leads to osteoclast apoptosis causing significantly reduced bone resorption without affecting bone formation.

-As a result, bone formation temporarily exceeds resorption and bone mass increases.

-After approximately 24 months, bone formation declines to the level of resorption and bone mass stabilizes.

-Over this time, bone mass increases 4% to 8% in the spine and 3% to 6% in the hip. This is accompanied by a 33% to 68% relative risk reduction for incident vertebral fractures and a 40% to 50% reduction in hip fractures (not with ibandronate) depending upon the bisphosphonate that is studied.

-Zoledronic acid may be the most effective attributable to its antiresorptive potency, intravenous (IV) administration, and compliance.



Omer Mala Ahmed Dear Dr Aliaa Omar El-hady
Regarding Bisphosphanates: <1% of oral Bisphosphonates are absorbed , then 50-60% of absorbed portion not bind to the bone & excreted unchanged in the Urine ?!

Aliaa Omar El-hady
Omer Mala Ahmedده تعليق والا سؤال يا د. عمر؟

Aliaa Omar El-hady

Clinical pharmacology

Bisphosphonates are characterised by poor intestinal absorption but highly selective localisation and prolonged storage in bone. Due to their stability the bisphosphonates are absorbed, stored and excreted unchanged.

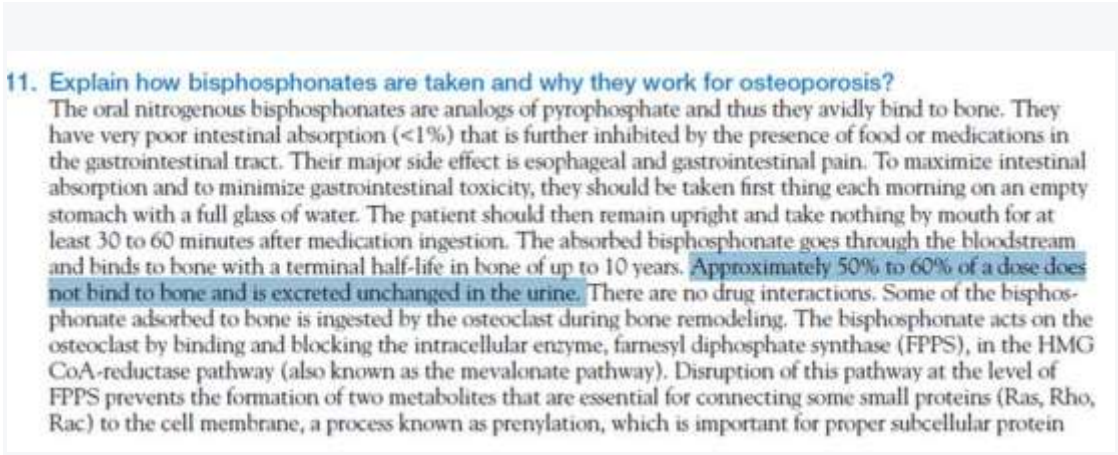
Absorption

Intestinal absorption is very low and variable (1-10%). It takes place by passive diffusion in the stomach and upper small intestine, and is reduced if the drug is given with calcium or iron. Bisphosphonates are therefore never given at meal times or with dairy products.

Clearance

With 20-80% of absorbed bisphosphonate rapidly taken up by bone and the remainder rapidly excreted in the urine, the half-life of bisphosphonates in the circulation is short (0.5-2 hours). Deposition in bone takes place at sites of bone

Aliaa Omar El-hady secrets 2015



11. Explain how bisphosphonates are taken and why they work for osteoporosis?

The oral nitrogenous bisphosphonates are analogs of pyrophosphate and thus they avidly bind to bone. They have very poor intestinal absorption (<1%) that is further inhibited by the presence of food or medications in the gastrointestinal tract. Their major side effect is esophageal and gastrointestinal pain. To maximize intestinal absorption and to minimize gastrointestinal toxicity, they should be taken first thing each morning on an empty stomach with a full glass of water. The patient should then remain upright and take nothing by mouth for at least 30 to 60 minutes after medication ingestion. The absorbed bisphosphonate goes through the bloodstream and binds to bone with a terminal half-life in bone of up to 10 years. Approximately 50% to 60% of a dose does not bind to bone and is excreted unchanged in the urine. There are no drug interactions. Some of the bisphosphonate adsorbed to bone is ingested by the osteoclast during bone remodeling. The bisphosphonate acts on the osteoclast by binding and blocking the intracellular enzyme, farnesyl diphosphate synthase (FPPS), in the HMG CoA-reductase pathway (also known as the mevalonate pathway). Disruption of this pathway at the level of FPPS prevents the formation of two metabolites that are essential for connecting some small proteins (Ras, Rho, Rac) to the cell membrane, a process known as prenylation, which is important for proper subcellular protein

Omer Mala Ahmed Thanks Dr Aliaa Omar El-hady for your information, sorry its a question & just i want to reassure, so that's why in some patients oral Bisphosphonates are not effective & then we shift to parenteral one & they get benefits. Thanks again for your always nice information 👉🏻👉🏻👉🏻

Aliaa Omar El-hady

BONE STRENGTHENING AGENTS - Bisphosphonates(11)

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Q-What precautions should be considered before prescribing bisphosphonates?

• Oral bisphosphonates are contraindicated in patients with esophageal problems (strictures, achalasia or severe dysmotility [scleroderma], varices), malabsorption, or inability to sit upright.

These are indications for an IV formulation.

• Oral bisphosphonates are contraindicated in patients with creatinine clearance (CrCl) <30 to 35 mL/min and IV bisphosphonates are contraindicated if CrCl <35 to 40 mL/min as a result of renal excretion.

Patients with severe stage 3 chronic kidney disease (CrCl = 35 to 40 mL/min) who are receiving IV bisphosphonates should be taken off drugs affecting renal function if possible (NSAIDs,diuretics), be well hydrated, and have slower infusion rates (ibandronate, 15 minutes; zoledronic acid, 60 minutes).

IV ibandronate is probably safer than IV zoledronic acid because of less effect on renal tissue.

• All invasive dental work should be performed before starting a bisphosphonate, if possible, to lessen future risk for osteonecrosis of the jaw.

• Make sure 25 OH vitamin D is >20 (preferably 30) ng/mL before starting therapy.

• IV bisphosphonates can cause a flu-like illness and bone pain lasting up to 2 to 3 days in 10% (ibandronate) to 30% (zoledronic acid) of patients. Premedication with acetaminophen will often prevent or lessen these symptoms.

• Compliance is important. Failure to take a bisphosphonate at least 70% of the time significantly decreases its fracture protection.

• BMD increase is less with low turnover and perimenopausal patients.

• Fracture protection has not been proven in osteopenic patients, especially less than age 65 years. Use FRAX to determine need for therapy.

• Bisphosphonates are contraindicated in patients who are pregnant or breastfeeding as a result of unknown effects on the developing skeleton.
In the rare patient who requires a bisphosphonate and may want to get pregnant in the future, risedronate may be the safest to use attributable to more rapid clearance from the blood after it is stopped. However, risedronate should be stopped 6 months before getting pregnant.

• Unusual side effects from bisphosphonates: ocular symptoms including uveitis, keratitis, optic neuritis, and orbital swelling have been reported.

Wafaa Elbana

حضرتك بتتكلمي عنهاdrugsلو ممكن الأسماء التجاريه تبقي مرفقه بكل للاستفادة

وشكرا مقدما لحضرتك

الدكتورعمر علي باجخيف what time is exactly to stop risedronate drug when planning to get pregnant?

BONE STRENGTHENING AGENTS - Bisphosphonates(12)

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Q-Is osteonecrosis of the jaw related to bisphosphonate therapy?

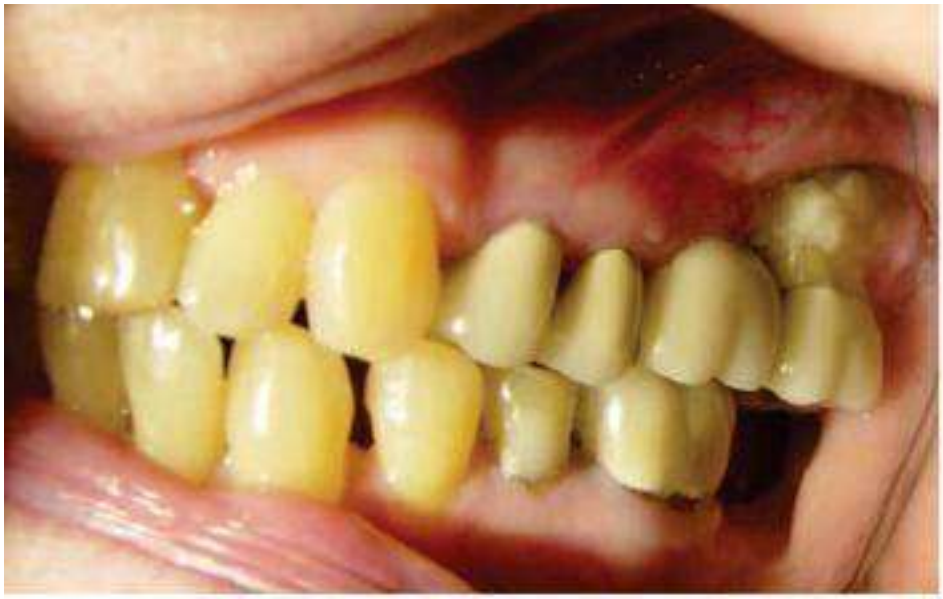
Osteonecrosis of the jaw (ONJ) presents as persistently exposed bone following an invasive dental procedure.

It occurs most often (up to 10% risk) during high dose IV bisphosphonate therapy for multiple myeloma or bone metastases.

ONJ has also been identified in some patients taking bisphosphonates for osteoporosis (0.3% risk).

Good oral hygiene and regular dental care are the best preventive measures.

Temporarily stopping bisphosphonates for invasive dental procedures (3 months before the procedure) is a common and reasonable practice but has not been shown to prevent ONJ. Some oral surgeons require a serum C-telopeptide to be in the
normal range before they will do surgery.



Bisphosphonate-Associated Osteonecrosis of the Jaws and Endodontic Treatment.Aaron P. Sarathy et al. JOE 31(10), Oct. 2005, 759-763

BONE STRENGTHENING AGENTS - Bisphosphonates(13)

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What about atypical femoral fractures with bisphosphonate use?

-Atypical femoral fractures have been reported in some patients on long-term bisphosphonate therapy (>5years).

-Any patient with unexplained thigh pain should be evaluated with a radiograph looking for a “bird beak” on the lateral aspect of the femoral shaft indicating a stress fracture.

-These fractures are frequently bilateral and may require femoral rods to stabilize.

-The risk appears low (1 in 2000 patients) but appears increased in active patients, those on corticosteroids, and those with very low bone turnover markers.

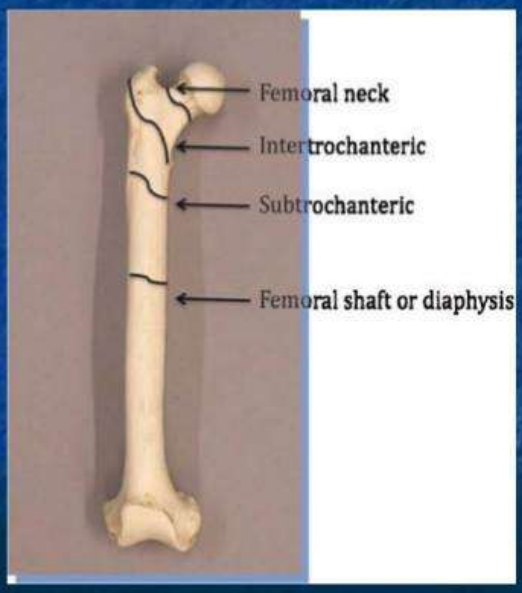
-Currently, no data exist regarding preventive measures.

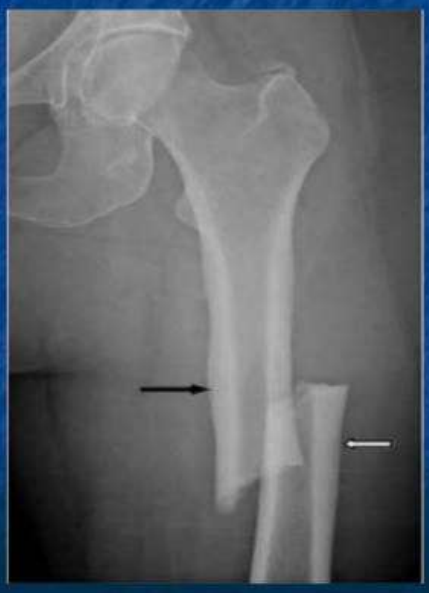
-After 5 years of bisphosphonate use, many providers recommend a 1-year to 2-year drug holiday for osteopenic patients and a temporary switch to an anabolic or other nonbisphosphonate agent for those with previous fragility fractures or very low BMD.

-It is also recommended that after 3 years of zoledronic acid, treatment should be stopped for the next 3 years.

-A drug holiday decreases the risk for atypical fractures by 70%.

Atypical fractures





BONE STRENGTHENING AGENTS - Bisphosphonates(14)
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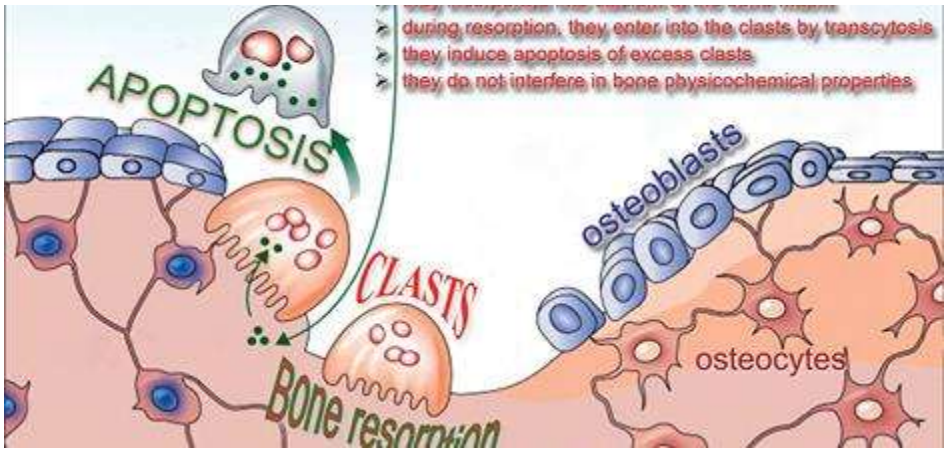

The use of bisphosphonates does not contraindicate orthodontic and other types of treatment!

1Full professor, School of Dentistry - University of São Paulo/Bauru and professor at the postgraduate program at the School of Dentistry -University of São Paulo/…
SCIELO.BR

BONE STRENGTHENING AGENTS - Bisphosphonates(15)

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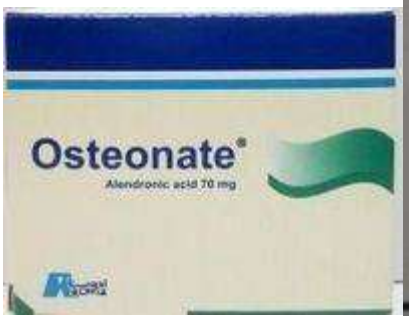
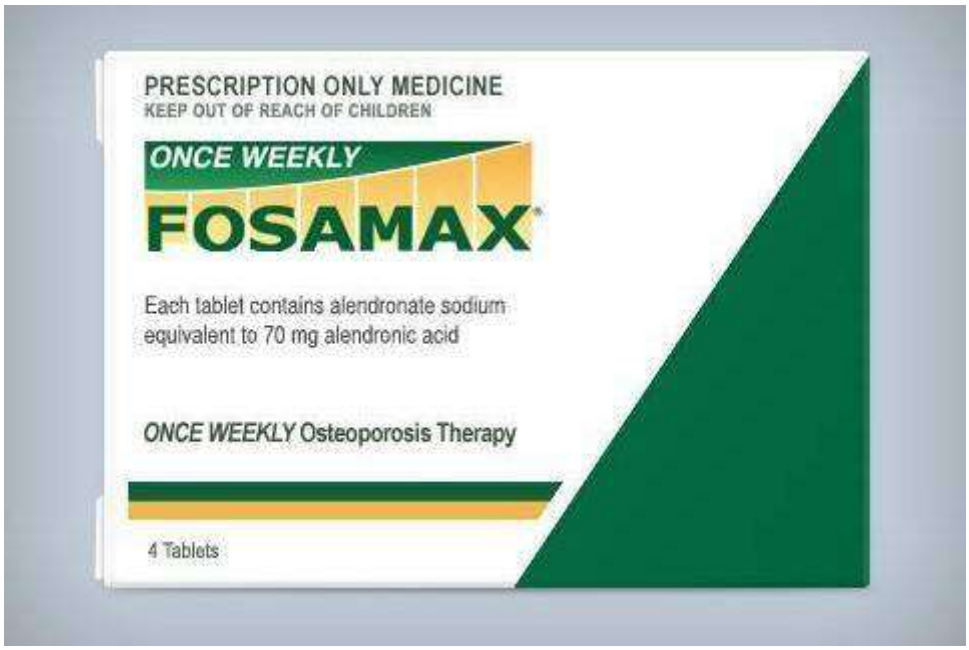
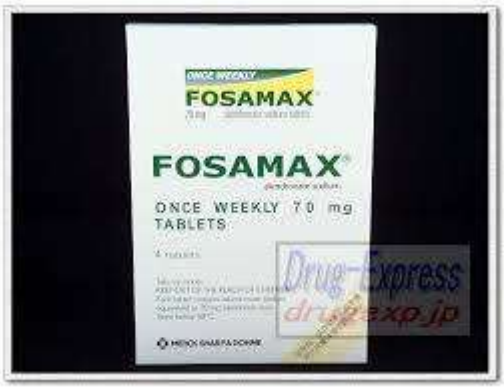
أمثلة لل alendronate فى السوق

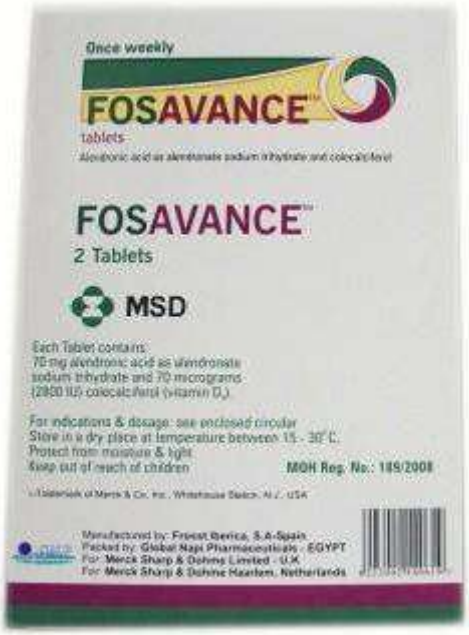

Sodium Alendronate Tablets BP
OSTEOZINO 70
Astral Pharmaceuticals
Sodium Alendronate Tablets BP
OSTEOZINO 70
Astral Pharmaceuticals
OSTEOZINO 70

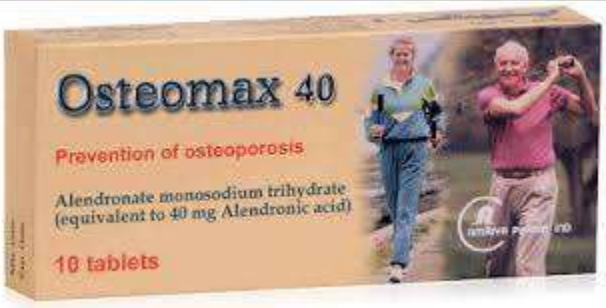

Osteonate®
Alendronic acid 70 mg


ألندوماكس بلس
pharmacia1
قرصين
pharmacia
specialized drugs & pharmaceuticals
حمض الأليندرونيك
٧٠ مجم
٢٨٠٠ وحدة دولية
فارماسيا
سيجما




ONCE WEEKLY
FOSAMAX
FOSAMAX
ONCE WEEKLY 70 mg
TABLETS
Drug-Express
drugexp.jp

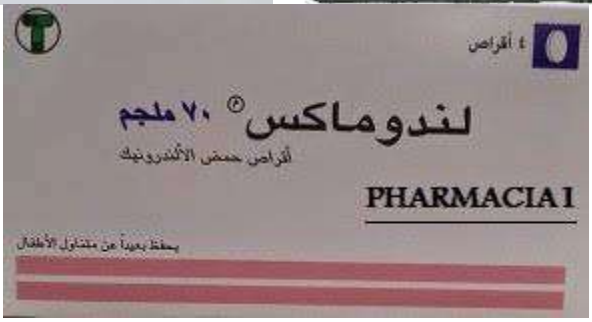

Once weekly
FOSAVANCE
tablets
FOSAVANCE
2 Tablets
MSD
Each Tablet contains
70 mg alendronic acid as alendronate
sodium trihydrate and 70 micrograms
(2800 IU) colecalciferol (vitamin D3).
For indications & dosage: see enclosed circular
Store in a dry place at temperature between 15 - 30° C.
Protect from moisture & light
Keep out of reach of children
MOH Reg. No.: 189/2008
Manufactured by: Frosst Iberica, S.A-Spain
Packed by: Global Napi Pharmaceuticals - EGYPT
For: Merck Sharp & Dohme Limited - U.K.
For: Merck Sharp & Dohme Haarlem, Netherlands


Osteomax 40
Prevention of osteoporosis
Alendronate monosodium trihydrate
(equivalent to 40 mg Alendronic acid)
10 tablets


Osteonate
For treatment of osteoporosis

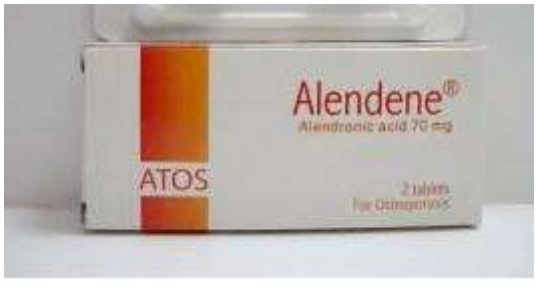

Debosteobone


10 Tablets
Sodium Alendronate Tablets
OSTEOFOS 10
Cipla
buy-pharma.com


٤ أقراص
لندوماكس® ٧٠ ملجم
أقراص حمض الأندرونيك
PHARMACIA1
يحفظ بعيداً عن متناول الأطفال


Bonapex
Alendronate
70
mg
Once Weekly


BONAPEX 10mg
APEX
30 Tablets


Alendene®
Alendronic acid 70 mg
ATOS

BONE STRENGTHENING AGENTS - Bisphosphonates(16)
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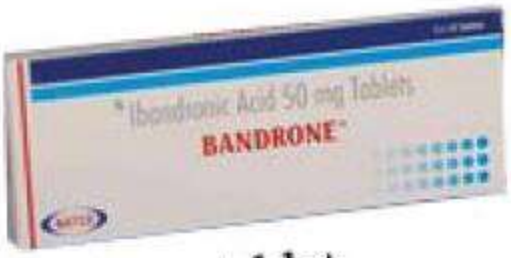
أمثلة لل ibandronate فى السوق

Bisphosphonates

- **Ibandronate (Boniva):** only FDA approved for use in the treatment (not prevention) of osteoporosis in post-menopausal women
  - **Not FDA approved for males**
    - Paucity of studies[1]
    - Similar pharmocokinetics in men and women[2]
    - Similar efficacy in men and women probable[3]
      (statement made in the Orwoll study)

Dr. Jenkins: the STRONG study is the only one of its kind that I could find for Ibandronate testing in males– in the speaker notes I wronte that it's "one of the only studies"– I hestistate to write "the only study" of its kind though—do you know of similar studies?



50 mg tablet

6 mg
Injection

50 mg tablet

6 mg
Injection


Mylan
NDC 0378-0215-02
Once-Monthly Pack
Once-Monthly
Ibandronate
Sodium
Tablets
150 mg*
PHARMACIST: Dispense intact with the enclosed Medication Guide to each patient.
Rx only
ONE 150 mg TABLET


1 Tablet
NDC 60505-2795-0
Once Monthly
Ibandronate
Sodium Tablet
150 mg*
Important Instructions
PHARMACIST: Dispense the Medication Guide provided separately to each patient.
USUAL DOSAGE: See package insert.
℞ Only
APOTEX CORP.


NDC 0591-3770-31
once-monthly
Ibandronate
Sodium Tablets
150 mg*
PHARMACIST: PLEASE DISPENSE WITH ATTACHED MEDICATION GUIDE.
Watson
3 Packs – One Tablet per Pack
Rx only

BONE STRENGTHENING AGENTS - Bisphosphonates(17)
==========
أمثلة لل residronate فى السوق

\


2 Film coated tablets
Risaldene® 35 mg
Once-a-Week


Actonel
risedronate sodium
Once a Week
35 mg
film-coated tablets
4 film-coated tablets


Actonel® 5mg
(risedronate sodium)


Osteoporosebehandlung
Risedronat Heumann 35 mg
Filmtabletten
Mononatriumrisedronat
N3/12 Filmtabletten
Zum Einnehmen
info@heumann.de
HEUMANN
Arzneimittel


4 Coated Tablets
RISEDOL 35mg
Risedronate Sodium 35 mg
Ibn Al Haytham Pharma - Industries Co. - Aleppo - Syria


30 Coated Tablets
RISEDOL 5 mg
Risedronate Sodium 5 mg
Ibn Al Haytham Pharma - Industries Co. - Aleppo - Syria


2 Film Coated Tablets
RISEDOL 75 mg


RISEDRONAT
SODIC ZENTIVA
35 mg comprimate filmate
Risedronat sodic
Un comprimat filmat conține risedronat sodic 35 mg
echivalent cu acid risedronic 32,5 mg
ZENTIVA
4 comprimate filmate


Risedronat Teva 35 mg
filmom obalené tablety
Nátriumrizedronát
12


Once Weekly
Risedronate Sodium Tablets 35 mg
RISOFOS
Cipla

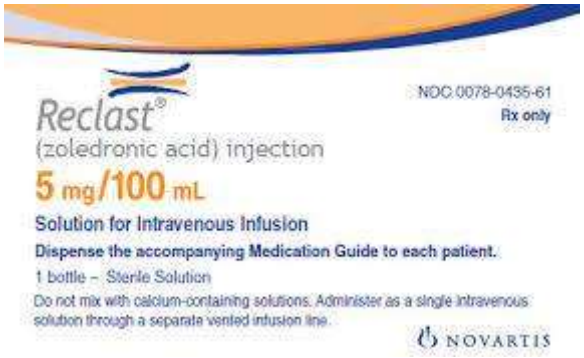
In generic products image may vary on the product received.

BONE STRENGTHENING AGENTS - Bisphosphonates(18)

==========

أمثلة لل zolendronic acid فى السوق


NOVARTIS
ZOMETA® 4 mg
Powder and solvent for solution for infusion/
Poudre et solvant pour solution pour perfusion/
Polvo y disolvente para solución para perfusión
Zoledronic acid
NOVARTIS
Zometa 4 mg
NOVARTIS


Reclast®
(zoledronic acid) injection
5 mg/100 mL
Solution for Intravenous Infusion
Dispense the accompanying Medication Guide to each patient.
1 bottle – Sterile Solution
Do not mix with calcium-containing solutions. Administer as a single intravenous solution through a separate vented infusion line.
NDC 0078-0435-61
Rx only
NOVARTIS


XOLNIC
LYOPHILIZED
KLAB
℞ ZOLEDRONIC ACID
FOR INJECTION 4 mg
XOLNIC
LYOPHILIZED
FOR SINGLE I.V. USE ONLY
झोल्नीक
KLAB
℞ ZOLEDRONIC ACID
FOR INJECTION 4 mg
XOLNIC
LYOPHILIZED
FOR SINGLE I.V. USE ONLY
झोल्नीक
KLAB

NDC 42023-163-01 **Rx only**

Zoledronic Acid Injection

5mg/100mL
(0.05 mg/mL)

Sterile Solution

Dispense the accompanying Medication Guide to each patient.

Solution for Intravenous Infusion

Do not mix with calcium-containing solutions.
Administer as a single intravenous solution through a separate vented infusion line.

100 mL Single - Dose Bottle

02/13

See package insert for
DOSAGE and ADMINISTRATION

Infusion time must not be less than 15 minutes.

Store at 25°C (77°F); [see USP Controlled Room Temperature]

Discard Unused Portion.

JHP PHARMACEUTICALS

Distributed by:
JHP Pharmaceuticals, LLC
Rochester, MI 48307

342023163011

EXP
LOT


DR. REDDY'S
DIN 02422433
1 x 100 mL Vial
sterile solution for intravenous infusion
Pr Zoledronic Acid Injection
5 mg/100 mL (0.05 mg/mL)
Bone Metabolism Regulator
DR. REDDY'S
DIN 02422433
1 x 100 mL Vial \ 1 x flacon de 100 mL
Pr Zoledronic Acid Injection
Pr Acide zolédronique injectable
Bone Metabolism Regulator
Régulateur du métabolisme osseux
sterile solution for i.v. infusion/ solution stérile pour perfusion i.v.


Aclasta
5 mg
infusionsvätska, lösning /
infuusioneste, liuos
Zoledronsyra /
Tsoledronihappo
NOVARTIS
Aclasta
5 mg
NOVARTIS
2027112

BONE STRENGTHENING AGENTS - SERMs (19)
==========
-The use of selective estrogen receptor modulators (SERMs) in the management of osteoporosis.
==========
-SERMs are agents that function as estrogen agonists in some
tissues (bone) and estrogen antagonists in other tissues (breast).

-Raloxifene (Evista) is a SERM that has been shown to improve bone mass and to reduce spine fractures; it is FDA-approved for the treatment of postmenopausal osteoporosis.

-Raloxifene has also been shown to reduce the risk (76%) of developing invasive breast cancer.

-The dose is 60 mg every day. Side effects include hot flashes, leg cramps, and an increased risk of thromboembolic disease (especially in smokers) similar to that seen with HRT.

-Raloxifene increases BMD by 2% to 3% in both the spine and hip while reducing the relative risk of vertebral fractures by 31% to 49% without an effect on hip fracture reduction.

-An ideal patient to receive raloxifene is an osteoporotic patient with a personal or family history of breast cancer.

-It can also be used in osteoporotic patients with chronic kidney disease, although little data are available to support its efficacy in this patient group.

Raloxifene is a selective estrogen receptor modulator (SERM) for osteoporosis.

Raloxifene

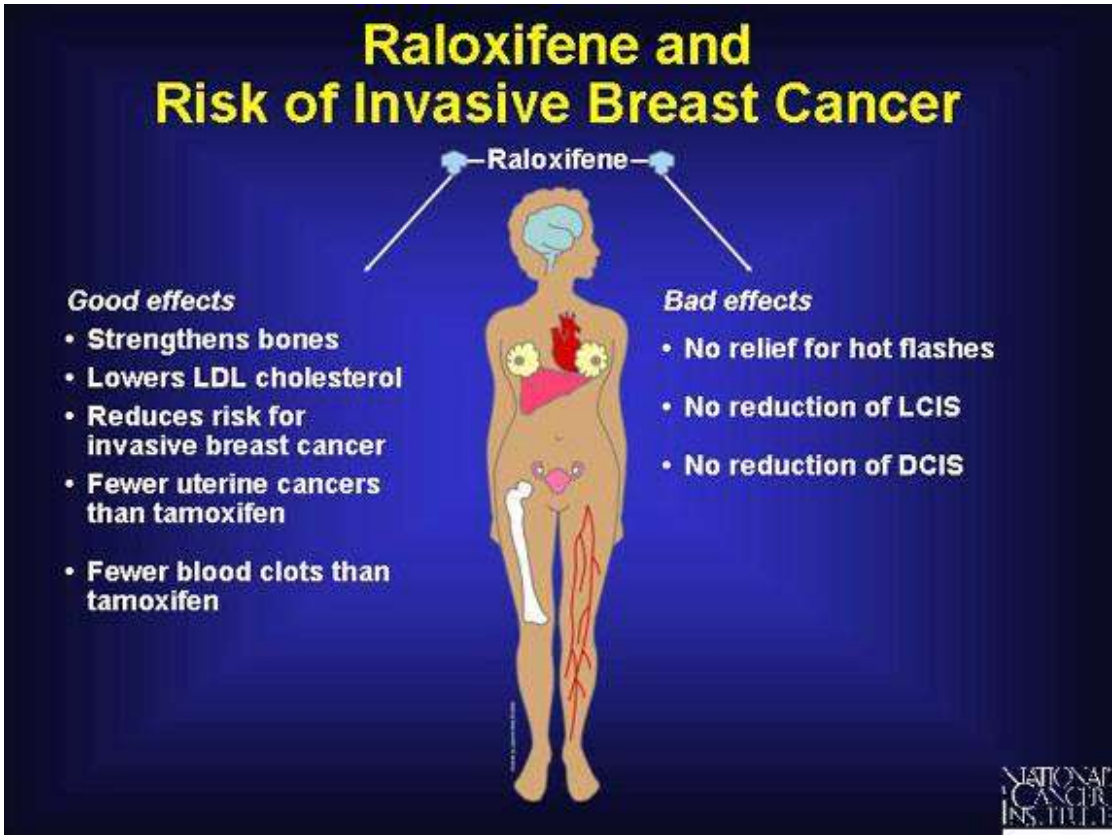
- Selective estrogen receptor modulator
- Acts as an estrogen agonist on bone
- Acts as an estrogen antagonist on breast and uterus
- Approved for prevention and treatment of postmenopausal osteoporosis
- Adverse events: Hot flashes, venous thromboembolism, leg cramps

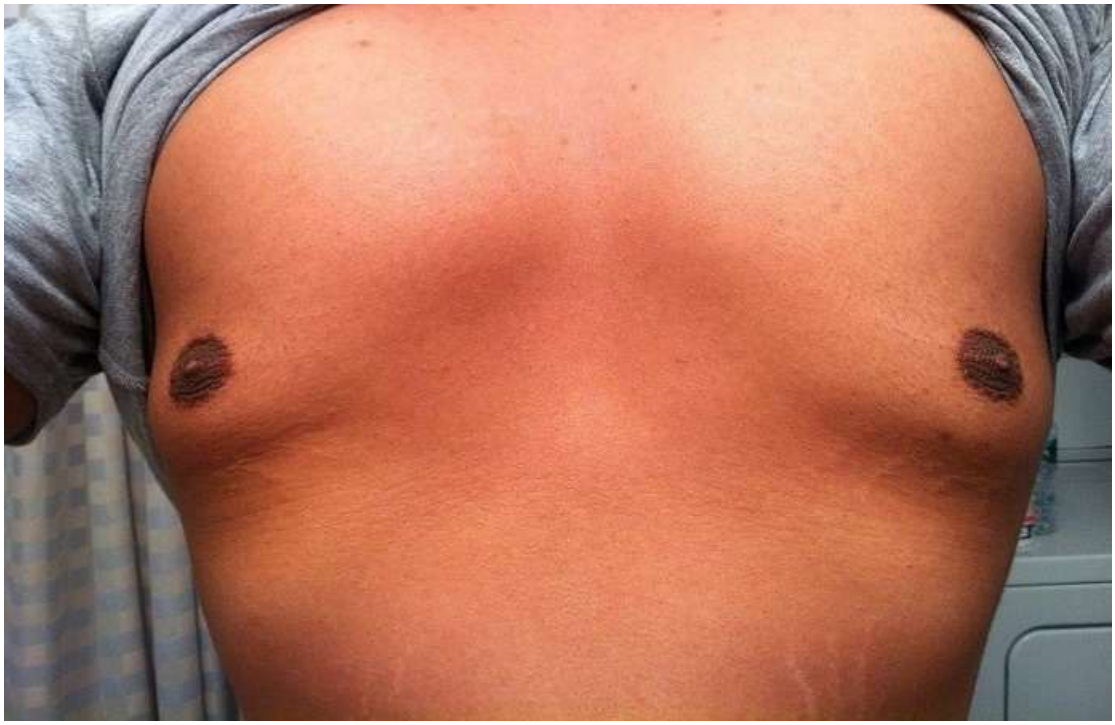
Raloxifene Hydrochloride. Physician's Desk Reference, 2005.

Raloxifene

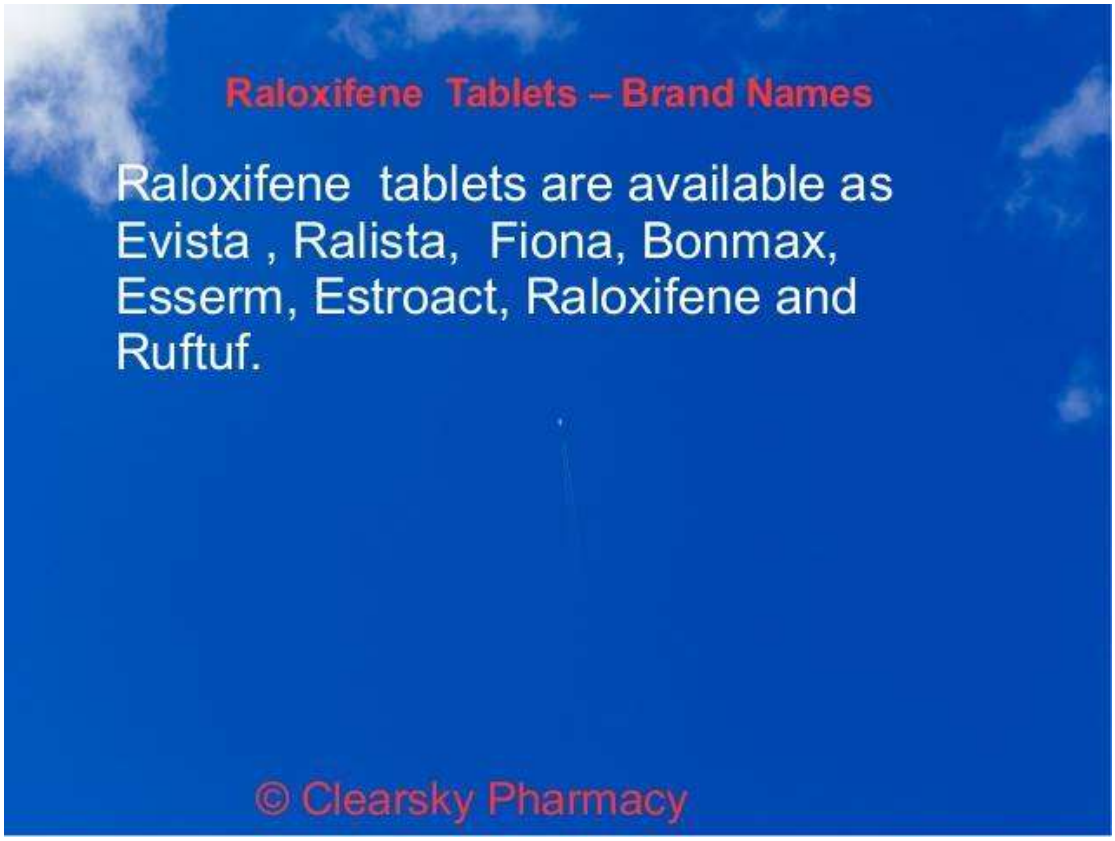
- **Mechanism of Action:** selective estrogen-receptor modulator,
  - **Benefits:** shown to increase BMD of hip and spine in women[1]
- **Application**: approved for treatment and prevention of osteoporosis in women; not approved for use in males[2].
- **Study disparities in males**
  - Narrow study contexts[3,5]
  - Raloxifene is understudied in males was not shown to significantly impact BMD in males[4]

Duschek study cited in the notes section is the only one I could find conducted in healthy males—the sample size was only 30 men! Is there another study out there that I'm missing?





BONE STRENGTHENING AGENTS - SERMs (20)
==========
أمثلة لل SERMs فى السوق




NDC 0093-7290-56
RALOXIFENE HYDROCHLORIDE Tablets USP
60 mg
PHARMACIST: Dispense the accompanying Medication Guide to each patient.
℞ only
30 TABLETS
TEVA
Each film-coated tablet contains 60 mg raloxifene hydrochloride, USP.
Usual Dosage: See package insert for full prescribing information.
Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.
Manufactured In Croatia By:
PLIVA HRVATSKA d.o.o.
Zagreb, Croatia
Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
N 3 0093-7290-56 8
Rev. B 6/2012


Razylan 60mg film-coated tablets
raloxifene hydrochloride
28 film-coated tablets
Razylan
60mg
film-coated tablets
raloxifene hydrochloride
Each film-coated tablet contains 60mg raloxifene hydrochloride equivalent to 56mg raloxifene
28 film-coated tablets


RALOXIFENE
POWDER
HO
S
OH
N
O
O


Liquid Ralox
60mL 60mg/mL
FOR RESEARCH PURPOSES ONLY.
NOT FOR HUMAN CONSUMPTION.
CEMPRODUCTS

Generic Evista (Raloxifene)

Osteoporosis, Women's Health, Cancer

Generic Evista is used for treating and preventing osteoporosis (bone thinning) in women who are past menopause. It is also used to reduce the risk of invasive breast cancer in certain women who are past menopause.

Brand(s): **Ralista**

Manufacturer: **Cipla**

Disease(s): **Osteoporosis / Breast Cancer / Menopause**

Known as: **Evista / Optruma**

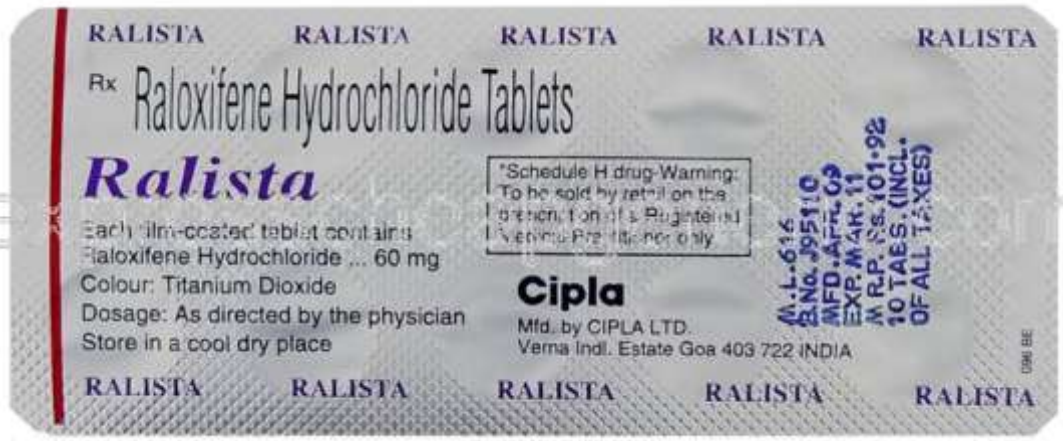

30 Tablets
Raloxifene Hydrochloride Tablets
Ralista
Cipla
Ralista


SOUTHERN SARMS
Raloxifene


Raloxifene
For Research
Purposes Only


RALOXIFENE
15 MG X
30 ML


10 x 10 Tablets
Cytotam 20
PHARMACY MEDICINE
KEEP OUT OF REACH OF CHILDREN
Cipla
Tamoxifen Citrate Tablets IP 20 mg
Cytotam 20
10 x 10 Tablets


RALISTA RALISTA RALISTA RALISTA RALISTA
Rx Raloxifene Hydrochloride Tablets
Ralista
Each film-coated tablet contains
Raloxifene Hydrochloride ... 60 mg
Colour: Titanium Dioxide
Dosage: As directed by the physician
Store in a cool dry place
*Schedule H drug-Warning:
To be sold by retail on the
prescription of a Registered
Medical Practitioner only
Cipla
Mfd. by CIPLA LTD.
Verna Indl. Estate Goa 403 722 INDIA
M.L.616
B.No. J95110
MFD. APR. 03
EXP. MAR. 11
M.R.P. Rs. 101.92
10 TAES. (INCL.
OF ALL TAXES)
RALISTA RALISTA RALISTA RALISTA RALISTA

As on oral administration, Raloxifene Hydrochloride undergoes extensive first pass metabolism resulting in poor bioavailability. The Objective of the present study was to prepare a matrix patch of Raloxifene Hydrochloride to increase its bioavailability. The main aim of the work is to provide a safe, single and alternative route of administration for the prevention of osteoporosis in post-menopausal women. This book gives insights into the innovative world of non invasive transdermal drug delivery. This compilation of work explains the preformualtion, formulation considerations, methodologies and evaluation parameters of developed system of transdermal patch. The book will serve as a guideline for the researchers in field of transdermal drug delivery.

Transdermal Matrix Patch

Iti Som
Meenakshi Bajpai
Yatendra Kumar

Transdermal Drug Delivery of Raloxifene hydrochloride

Formulation and Evaluation of Transdermal matrix Patch

Iti Som,M.Pharmis currently an Assistant professor of Pharmaceutics at ITS Pharmacy College(Ghaziabad,India). She has supervised M.Pharm research projects during her 5 years of academic experience. She has credited scientific publications in reputed journals.Her area of interest includes Drug delivery systems and Intellectual property rights.

978-3-8443-2987-2

Som, Bajpai, Kumar

LAP LAMBERT Academic Publishing

BONE STRENGTHENING AGENTS - Denosumab (Prolia) (21)

==========

-Denosumab (Prolia) is a monoclonal antibody directed against RANK-L.

-This interferes with the ability of osteoblasts (and other cells with RANK-L on their surface) to bind to RANK and stimulate osteoclastic bone resorption.

-Denosumab is given in the clinic at a dose of 60 mg SC every 6 months.

-This medication is well tolerated, although there is a concern that infections could be increased because RANK-L is also on T helper cells and involved in dendritic cell activation. In trials, denosumab increased lumbar spine bone mass by 6.5% and hip mass by 3.5%.

-This was accompanied by a 68% reduction in vertebral and 40% reduction in hip fractures over 3 years.

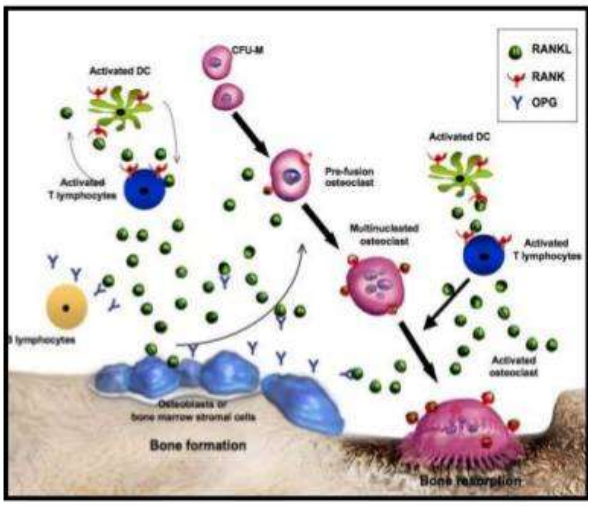
-Because of lack of accumulation in bone, it is hoped that the incidence of ONJ and atypical femur fractures will be less, although both complications have been reported in patients on denosumab.

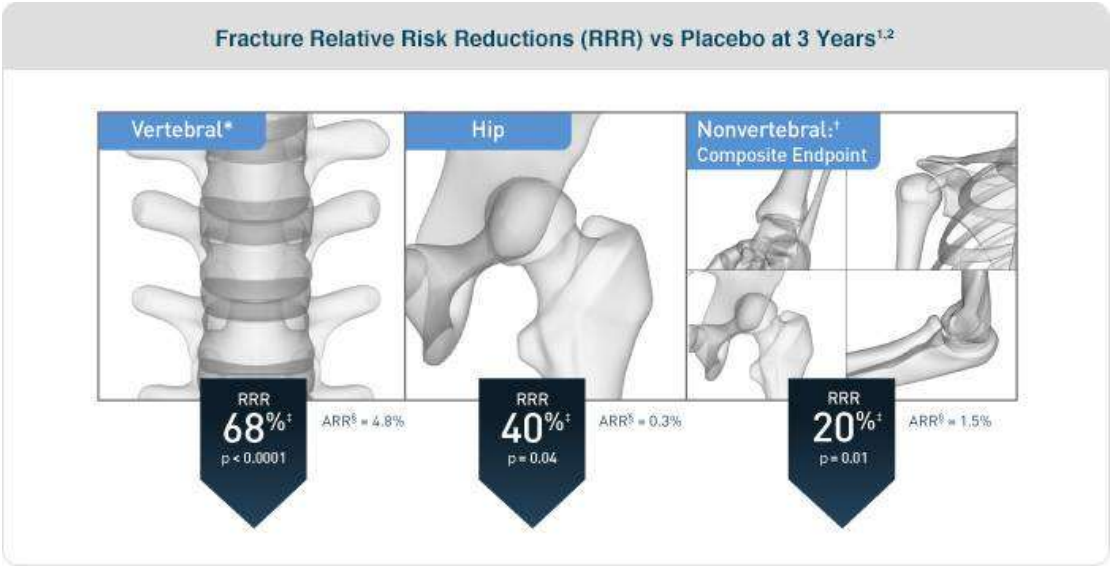
-Denosumab is cleared by the reticuloendothelial system and can therefore be used in osteoporotic patients with stage 4 chronic kidney disease (CrCl = 15 to 30 mL/min).

-Patients with chronic renal disease are most likely to get hypocalcemia with denosumab use and should be warned of
this complication.

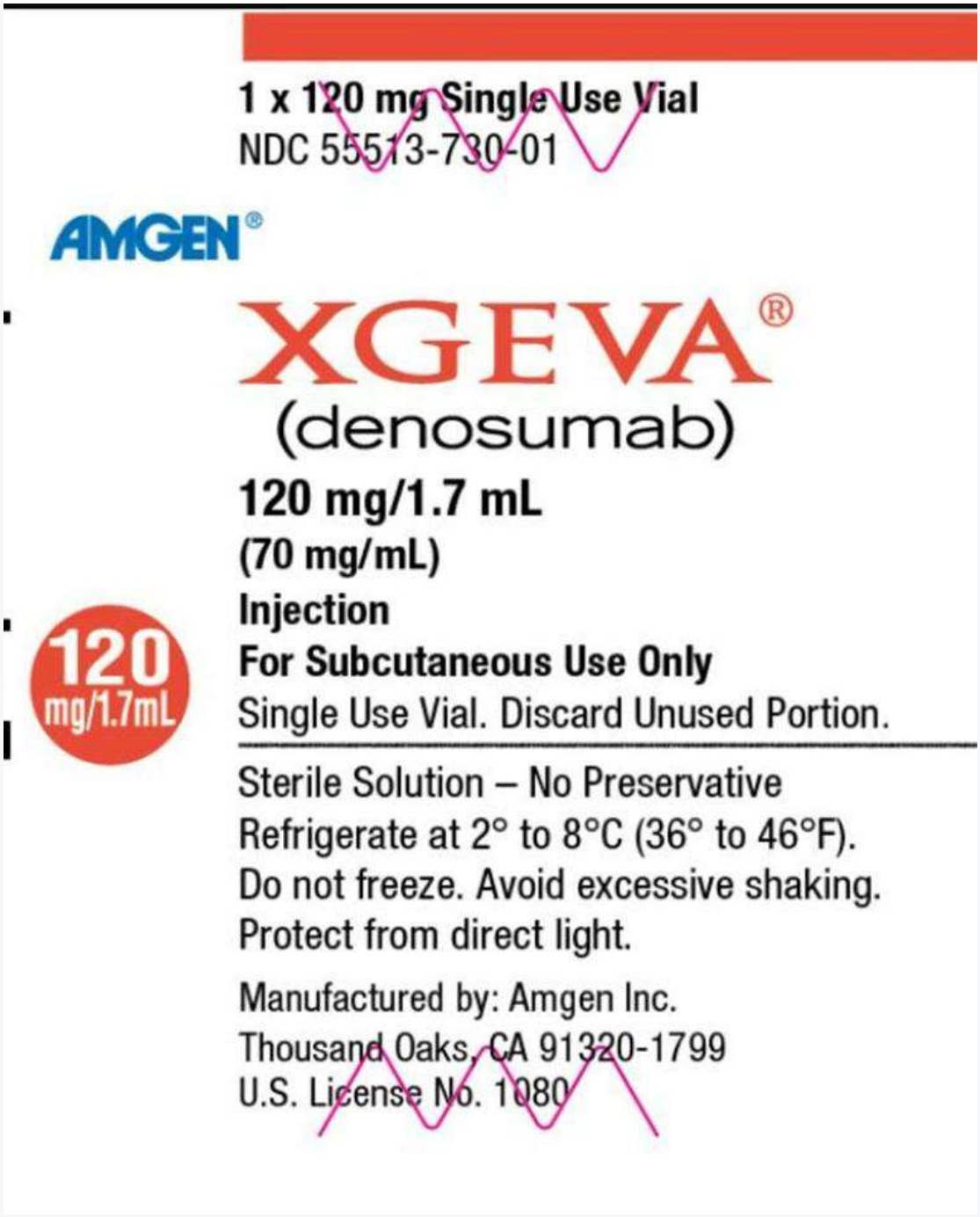
Prolia (Denosumab)

- Biologic from Amgen supposedly better than others because:
  - Targeted mechanism – RANKL inhibitor
    - Inhibits formation and function of osteoclasts
  - Improved dosing schedule
    - s.c. once every 6 months
  - Superior tolerability
  - Reduced fracture risk by 68%
  - Cost >$10,000/year
- August 2009 FDA panel:
  - Data from 30 clinical trials
  - Only 2 of 6 indications
    - Safety issues





Tamer Elfarahaty It is FDA approved on June , 2010 for prevent skeleton related events in bone metastasis .It is manufactured by the same company of Prolia (Amgen)



الدكتورعمر على باجخيف most common side effect of denosumab are back pain, pain in your arms and legs, high cholesterol, muscle pain, and bladder infection

BONE STRENGTHENING AGENTS - parathyroid hormone (PTH) (22)

==========

Q-How can parathyroid hormone be an anabolic agent for treating osteoporosis?

==========

-Persistently elevated serum parathyroid hormone (PTH) levels (primary hyperparathyroidism) promote osteoclastic bone resorption and bone loss.

-In contrast, intermittent daily pulses of exogenous PTH actually
stimulate osteoblast differentiation, proliferation, and survival resulting in osteoid formation and increased bone mass.

-It also decreases the production of the bone inhibiting protein, sclerostin, from osteocytes.

-Teriparatide (forteo) is a 34 amino acid fragment of intact PTH that retains the ability to bind to and activate PTH receptors on osteoblasts and osteoblast precursors.

-It is self-administered daily at a 20-μg/day dose SC for 18 to 24 months.

-In trials, teriparatide increased lumbar spine bone mass by 9% to 13% and hip bone mass by 2.5% to 5% while decreasing the relative risk of new vertebral fractures by 65% and nonvertebral fractures by 50%.

-The most common side effects are similar to placebo and include headache, nausea, arthralgias,orthostasis, and flushing.

FORTEO®

teriparatide (rDNA origin) injection

20-mcg daily dose in a 2.4-mL prefilled delivery device

Teriparatide (Forteo)

FORTÉO™ teriparatide injection (rDNA origin)

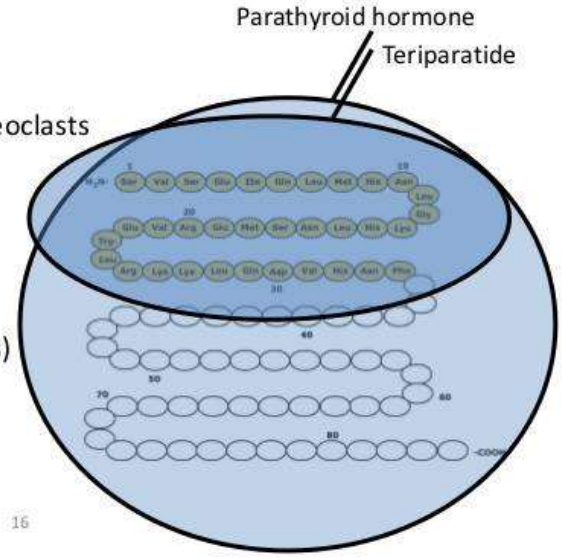
- Parathyroid Hormone
- Dosing: 20mcg SC daily for up to 2 years
  - Can self-inject in abdomen or thighs
- FDA approved for treating osteoporosis in postmenopausal men and women at high risk of fracture
- Fracture prevention: Spine and other bones
- Possible s/e: Nausea, dizziness & cramps
- Renal dosing: None
- Contraindications: Paget's Disease (unexplained elev. ALP), young patients with open epiphyses, prior external beam or implant radiation involving the skeleton, & patient's w/ current or h/o bone malignancies/metastases
- Monitoring considerations: After 4 months of therapy, repeat serum Ca, albumin & Vit D 25-OH levels. Do not check a iPTH it will be elevated & do not repeat a DXA in 1 year, wait at least 18 months.

Teriparatide (Forteo)

- 34 amino acid analog of parathyroid hormone
- 20 µg s.c. once/day
  - Thigh or abdomen

- Enhances bone strength and size
  - Intermittent exposure
    - → activates osteoblasts > osteoclasts
  - Chronic exposure
    - → enhances bone resorption
    - 2nd line therapy
    - Only used for 2 years

- Major side effect: bone cancer (in rats)
- Cost: $7,000/year



Teriparatide [rDNA origin]

Teriparatide is an anabolic agent with a unique mechanism of action compared to that of currently available antiresorptive therapies.

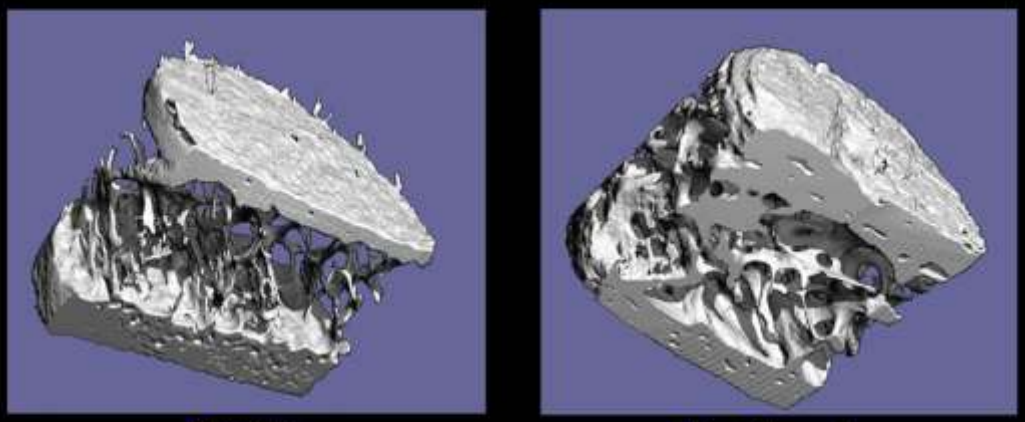
ACTION: Works through a normal physiologic pathway via PTH receptors on bone

EFFECT: Increases bone remodeling

RESULT: Bone formation significantly exceeds bone resorption

OUTCOME: Increase in skeletal mass and bone strength

FORTEO® (teriparatide [rDNA origin] injection) Stimulates New Bone Formation



Baseline | After 21 months

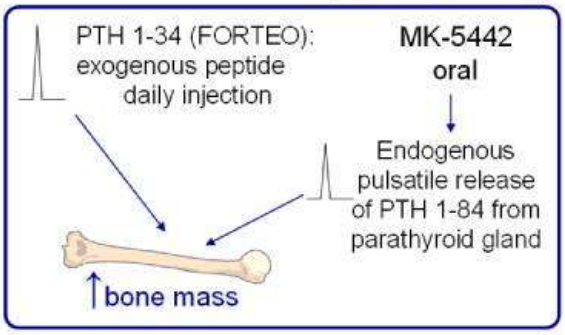
These microCT images of iliac crest bone biopsies were obtained from a 65-year-old woman who had a BMD response that is representative of the treatment group.[1] FORTEO forms normal-quality bone (as shown by lack of woven bone and marrow fibrosis).

1. Data on file, Lilly Research Laboratories.

Calcium-Sensing Receptor Regulates Physiological Parathyroid Hormone Release

Japan Tobacco

- FORTEO (PTH fragment 1-34) is the only FDA-approved osteoanabolic[1]
  - Daily subcutaneous injection provides desired short-term duration of PTH action
- Calcium-sensing GPCR regulates parathyroid hormone (PTH) release from the parathyroid gland



- MK-5442 (JTT-305) is a novel oral osteoanabolic agent that stimulates the release of a pulse of endogenous PTH (1-84) with short-term action by blocking the calcium-sensing receptor in the parathyroid gland
  - Positive proof of concept established in a 12-week Phase IIa study
  - Phase IIb clinical program underway in Japan
  - Worldwide program anticipated to initiate in 2009

[1] Black D et al. NEJM 2003 Sep 25; 349(13):1207-1215

MERCK

14


1 x 1 Cartridge
Rx
TERIPARATIDE [rHu PTH (1-34)] INJECTION
TERIFRAC (r-DNA origin) 750 mcg / 3 ml
Terifrac
टेरीफ्रैक
For Subcutaneous use only


FORTEO

BONE STRENGTHENING AGENTS - parathyroid hormone (PTH) (23)

==========

Precautions before prescribing teriparatide:

==========

• Teriparatide is contraindicated in patients at increased risk for osteosarcomas: Paget's disease, unexplained alkaline phosphatase elevation, children and young adults with open epiphyses, previous external beam or implant radiation therapy involving the skeleton.

• In patients without contraindications, teriparatide does not cause an increased risk of osteosarcomas compared to the general population (1:250,000).

• Use in patients with skeletal metastases and myeloma is contraindicated.

• May cause hypercalcemia (digoxin toxicity, kidney stones) and hyperuricemia (gout).

• Expensive. It is cost effective when used in patients at highest risk for osteoporotic fractures (T-score < –2.5 to –3.0 with history of fragility fracture; T-score ≤ –3.0) or in patients who develop a fragility fracture while on an oral bisphosphonate.

• Teriparatide can help heal stress fractures (especially sacral, pelvic), nonunion fractures, and ONJ.

• Teriparatide is usually not used concurrently with an antiresorptive agent as a result of blunting of the anabolic response. This is most applicable to patients who have previously received prolonged antiresorptive therapy before starting teriparatide. In patients who are started without previous exposure to antiresorptives, the simultaneous use of teriparatide and IV zoledronic acid may be better than either one alone.

• A PTH level should be checked before use. If elevated, secondary causes (vitamin D deficiency) should be corrected to normalize the PTH level. The benefit of

teriparatide in patients with persistent mild elevations of PTH is unclear but many experts feel it can still be effective. It can be used in patients with severe kidney disease but the effectiveness in these patients (who frequently have an elevated PTH) is unknown.

• After treatment with teriparatide, an antiresorptive agent should be started to preserve the gains in bone mass.

• After one 2-year course of teriparatide, a subsequent course in patients with severe osteoporosis is presently being studied (intermittent osteoanabolic therapy).

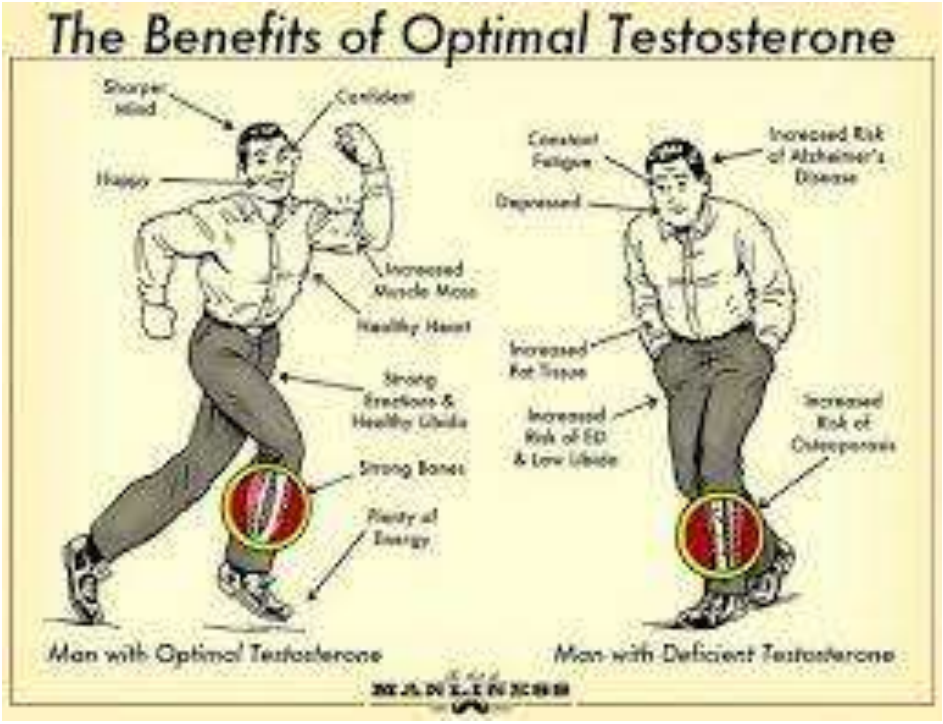
Omer Mala Ahmed Thanks for this big information dear Dr Aliaa
But if the patient was on Anti-Resorptive drugs (Bisphosphonates) for long periods & not got benefit from them , as you know these drugs remain in bones for a long periods, so when we decide to shift to Teriparatide in these cases , does it be effective? Thanks allot

BONE STRENGTHENING AGENTS - testosterone (24)
==========
Q-Discuss the role of testosterone for the treatment of osteoporosis?
==========
-Men with osteoporosis and symptoms of hypogonadism may benefit from testosterone replacement therapy, especially if the level is <150 ng/dL.

-Testosterone can be administered intramuscularly (100 to 200 mg every 1 to 2 weeks) or as a transdermal patch (AndroDerm) or cream (Testim, AndroGel, Axiron,Fortesta).

-This therapy can increase bone mass but also increases risk of prostate cancer.

-Patients without improvement in hypogonadal symptoms should not continue because other therapies for osteoporosis are more beneficial.




NDC 0009-0417-02
10 ml Vial
Depo®-Testosterone
testosterone cypionate
200 mg per ml


Clear, colorless gel provides transdermal delivery of testosterone through the skin of the shoulders, and upper arms*
30 Unit-dose Packets
NDC 0051-8462-30
Contains 40.5 mg of testosterone in 2.5 Grams of gel per unit dose
AndroGel®
(testosterone gel) 1.62%
Rx Only
For Topical Use Only
Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure.
Dispense the enclosed Medication Guide to each patient.
abbvie

BONE STRENGTHENING AGENTS (25)

==========

Algorithm for the management of osteoporosis.

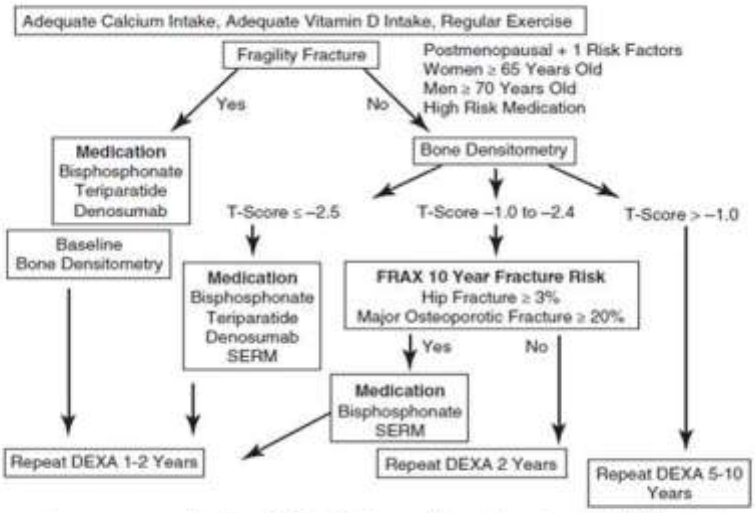


Figure 87-3. Osteoporosis management algorithm. *DEXA*, Dual-energy X-ray absorptiometry; *SERM*, selective estrogen receptor modulator.